Nanofibrillar Surfaces Promote Rac Activation and Self-Renewal in Mouse Embryonic Stem Cells

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The regulation of embryonic stem cell fate is controlled by the interplay of signaling networks that either promote self-renewal or induce differentiation. Leukemia inhibitory factor (LIF) is a cytokine that has been demonstrated to be a requirement for stem cell renewal in mouse but apparently not in human embryonic stem cells. However, feeder layers of embryonic fibroblasts are capable of inducing stem cell renewal in both cell types, suggesting that for human embryonic stem cells, the self-renewal signaling pathways may be promoted by other triggers, such as chemical or physical components of the extracellular matrix (ECM) of the feeder cells. We have recently developed a synthetic nanofibrillar matrix whose three-dimensional (3D) organization resembles the structure of the ECM/basement membrane. Growth of mouse ESCs on these 3D surfaces greatly enhanced their proliferation and self-renewal and their expression of nanog. This enhancement was correlated with an increase in the activation of the small GTPase Rac as well as PI3 kinase. Overexpression of a dominant negative mutant of Rac inhibited the growth of mouse embryonic stem cells cultured on nanofibers, and inhibition of PI3 kinase lead to downregulation of nanog. These results provide support for a view of stem cell signaling in which geometry, in particular, the three dimensionality of the culture surface, is an important component of signal transduction pathways.